(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076518 A1

(51) International Patent Classification[7]: A61L 15/00, 15/14, 15/60

(21) International Application Number: PCT/GB02/01573

(22) International Filing Date: 27 March 2002 (27.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0107655.3 27 March 2001 (27.03.2001) GB

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; 345 Park Avenue, New York, NY 10154 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHEN, Wai, Yuen, John** [GB/GB]; 34 Strawberry Lane, Wilmslow, Cheshire SK9 6AH (GB). **CLAY, Christopher, Stanley** [GB/GB]; 6 Linden Drive, Mickle Trafford, Chester CH2 4QT (GB). **WALKER, Michael** [GB/GB]; Homeleigh, Brynsannan, Brynford, Flintshire CH8 8AX (GB).

(74) Agent: **BARKER BRETTELL**; 10-12 Priests Bridge, London SW15 5JE (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/076518 A1

(54) Title: WOUND DRESSING

(57) Abstract: A water-absorbent, composite material which comprises i) at least 30 %, by weight of the composite material, of an alginate in admixture with: ii) a hydrogel-forming, synthetic, non-polysaccharide polymer; and/or iii) a mixture of at least two hydrogel-forming polymers different from (ii).

WOUND DRESSING

This invention relates to the dressing of wounds; more particularly, the present invention relates to the dressing of chronic wounds using materials not customarily regarded as pharmaceutical agents.

It is known that, in chronic wounds, a large number of endogenously produced factors are released into the wound. It is believed by some workers in this field that the abnormalities of tissue repair demonstrated in chronic wounds may, at least in part, be due to the over-activity of tissue degradation mechanisms mediated by some of these factors.

In particular, there is evidence to suggest that proteolytic enzymes may be implicated in the pathogenesis of chronic wounds. Thus, it is believed that the presence of proteases produced in the wound may result in extensive extra-cellular matrix degradation to dermal components such as collagens and proteoglycans.

This invention seeks to reduce the effect of at least certain proteases in frustrating the healing of chronic wounds.

According, therefore, to a first aspect of this invention, there is provided a water-absorbent, composite material which comprises:

i) at least 30%, by weight of the composite material, of an alginate in admixture with:

ii) a hydrogel-forming, synthetic, non-polysaccharide polymer; and/or

iii) a mixture of at least two hydrogel-forming polymers different from ii).

In the composite material of the invention the alginate may comprise at least 40%, preferably at least 50%, by weight of the composite material. Suitably, the alginate may have been rendered insoluble. Desirably, the alginate may comprise a major amount of mannuronic (high-M) moieties.

Component ii) of the composite material of the invention may comprise homo- or copolymer of N-vinyl pyrrolidone, acrylamide or ethylene oxide. One of the components iii) may comprise a semi-synthetic derivative of cellulose. One of the components iii) may comprise cellulose, hyaluronic acid or a pectin. Component iii) may comprise a mixture of two or more such components or at least one such component with a semi-synthetic derivative of cellulose.

The composite material of the invention suitably may have at least one of the components of i), ii) and/or iii) in a fibrous form; for example wherein at least two of the components are preparable by co-spinning. The material may be felted. The material may be woven or knitted.

This invention also provides a wound dressing which comprises a composite material as herein disclosed.

According to a further aspect of this invention there is provided use of a composite material or polymer which is swellable in aqueous media for the manufacture of a wound dressing comprising the composite material or polymer to reduce the concentration of proteolytic enzyme in a wound by application of the wound dressing externally thereto.

Preferably in such use, the composite material is as herein defined. Thus the polymer may be a substituted or unsubstituted, homo- or co-polysaccharide. Suitably, the polymer may comprise uronic acid groups. Desirably, the substituted polysaccharide may comprise etherified or

acylated hydroxyl groups, and/or may comprise esterified uronic groups. In particular, the substituted polysaccharide may comprise at least some hydroxyl groups which have been replaced by amino or acylated amino groups.

The aforementioned substituent may comprise a saturated or unsaturated, carbocyclic or heterocyclic, mono- or polycyclic group. The unsaturated group may include an aromatic group. Suitably, the polycyclic group may comprise a fused polycyclic structure. The polymer may be cross-linked. It may be formed as a film or as a fibre. Furthermore, a mixture of polymers as herein defined may be used in the manufacture of the wound dressing. When the polymer, or at least a component in a mixture of polymers, is formed as a fibre, the fibres may be disposed in the wound dressing manufactured therefrom as a non-woven mat or as a woven fibre. The materials in the wound dressing manufactured therefrom may be associated with one or more non-water swellable materials.

This invention also provides the use of a polymer as herein defined as a wound dressing agent.

This invention further provides a method of treatment of the human body, which method comprises applying externally to a wound on the body a wound dressing which comprises a composite material or a polymer which is swellable in aqueous media, the application thereby reducing the concentration of proteolytic enzymes in the wound. Desirably, the composite material or the polymer is herein defined.

While it is intended that the wound dressings in accordance with the present invention may be used without preservations or pharmacologically active ingredients, it is possible to include these in minor amount. For example, an antibiotic or anti-microbial agent such as metronidazole,

silver sulphadiazine, neomycin or penicillin; antiseptic agents such as povidone iodine; anti-inflammatory agents such as hydrocortisone or triamcinolone acteonide; or skin protective agents such as zinc oxide may be included.

The following Examples illustrate the invention in which reference is made to the following figures:

Figure 1 shows the % elastase activity remaining in solution after incubation for 3 hours with AQUACEL®. The control was incubated without AQUACEL®.

Figure 2.1 shows the % elastase activity remaining in solution after incubation for 3 hours with alginate (Kaltostat®, ConvaTec). The control was incubated without alginate.

Figure 2.2 shows the amount of elastase activity that is recovered in the washing supernatant is significantly lower in Kaltostat® than the comparator dressing materials.

Figure 3 shows the % elastase activity remaining in solution after incubation for 3 hours with high-M alginate (Kaltogel™, ConvaTec).

Figure 4.1 shows the % elastase activity remaining in solution after incubation for 1 hour with various alginate-containing preparations.

Figure 4.2 shows the amount of elastase activity that is recovered in the washing supernatant in formulation AC6040 is negligible and significantly lower in comparison to pure preparations of alginate (A100) and pure sodium CMC (C100), which are in turn lower than the comparator gauze dressing and Allevyn™.

Figure 5 shows the amount of elastase activity that is recovered in the washing supernatant in formulations ACL404020 and AC6040 (Example 4) is negligible and significantly lower in comparison to pure preparations of alginate (A100) and pure sodium CMC (C100), which are in turn lower than the comparator gauze dressings and Allevyn™.

Figure 6.1 shows the % elastase activity remaining in solution after incubation for 1 hour with various alginate-containing preparations.

Figure 6.2 shows the amount of elastase activity that is recovered in the washing supernatant of Alginate/PVP composition is comparable to those of the comparator dressing materials, in this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially-available surgical dressing (Allevyn™).

Figure 7.1 shows the % elastase activity remaining in solution after incubation for 1 hour with various preparations. All incubations were carried out with the same incubation volume to material weight ratio.

Figure 7.2 shows the amount of elastase activity that is recovered in the washing supernatant of Alginate/CMC/HYAFF composition is comparable to those of the comparator dressing materials.

Figure 8.1 shows the % elastase activity remaining in solution after incubation for 1 hour with the various preparations.

Figure 8.2 shows the amount of elastase activity that is recovered in the washing supernatant of Alginate/CMC/pectin composition is comparable to those of the comparator dressing materials.

Figure 9.1 shows % elastase activity remaining in solution after incubation for 1 hour with the various preparations.

Figure 9.2 shows the amount of elastase activity that is recovered in the washing supernatant of Alginate/PEO composition is comparable to those of the comparator dressing materials.

Figure 10.1 shows the % elastase activity remaining in solution after incubation for 1 hour with the various preparations.

Figure 10.2 shows that the amount of elastase activity that is recovered in the washing supernatant of pectin mixture composition is comparable to the comparator dressing materials.

Figure 11.1 shows the % elastase activity remaining in solution after incubation for 1 hour with the various preparations.

Figure 11.2 shows the amount of elastase activity that is recovered in the washing supernatant of pectin/CMC composition is less than those of the comparator dressing material.

EXAMPLE 1

Pure sodium carboxymethyl cellulose (CMC) fibres (AQUACEL®, ex ConvaTec) gel upon hydration, the water being absorbed into the fibres. In experiments where AQUACEL® is soaked in an excess of fluid containing elastase, AQUACEL® is shown to concentrate the elastase in the supernatant, indicating absorption of water in preference to proteinaceous substances in solution. However, this test methodology is not directly applicable to clinical conditions where dressings are normally applied in excess of wound exudate. In an alternative approach, solutions containing elastase were applied to test materials comprising both AQUACEL® and also to comparator dressing materials so that the solutions were entirely soaked into the dressing without leaving any supernatant. These dressing materials were then washed and the amount of elastase detected in the wash solution gave an indication of how much elastase was retained in the dressing material.

Elastase solution from a bacterial source *Pseudomouas aeruginosa* (100 µl aliquots, 2.34 µU/ml) was applied to 1 cm^2 square pieces of each of the test materials. The solution was allowed to soak in for five minutes. The material was then washed with 1 ml of phosphate buffered saline for 1 hour at room temperature. Aliquots of the supernatant were next withdrawn to assay for elastase activity by an azocasein method whereby the hydrolysed azocasein releases a soluble coloured product that can be measured by standard spectiophotometric methodology. The comparator dressing materials were two gauze materials (standard surgical gauze and NA™ gauze ex Johnson + Johnson) and a highly absorbent commercially available surgical dressing (Allevyn™ ex Smith + Nephew).

Results demonstrate that the amount of elastase activity that was recovered in the washing supernatant was significantly lower in AQUACEL® than the comparator dressing materials. Figure 1 shows the % elastase activity remaining in solution after incubation for 3 hours with AQUACEL® (column B). The control, column A, shows incubation without AQUACEL®.

It is believed, though not ascertained, that AQUACEL® forms a cohesive gel upon hydration. Initial uptake of the proteinase solution into AQUACEL® is likely to be by capillary absorption. Water is then absorbed into the CMC fibres with a consequent closing of the inter-fibre space, trapping the proteins there. The protein is difficult to wash out thereafter because of its physical entrapment.

AQUACEL®, NA™ and ALLEVYN® are trade marks.

EXAMPLE 2

Calcium alginate (Kaltostat® ex ConvaTec) is found to have the ability to absorb elastase *in vitro*.

The test materials were cut to provide a small amount of material (5 mg) which was then incubated at room temperature with 1.5 ml of the elastase solution containing 50 μU/ml. The elastase solution consisted of purified human neutrophil elastase (Calbiochem) in 50 mM Tris-HCl and 0.05% triton X-100 buffer at pH 8.0. At the end of the incubation period of 3 hours, a small aliquot of the supernatant was reacted with Elastase Substrate 1 (a calorimetric substrate: Calbiochem) in a Cobas Fara II auto-analyser to determine the activity concentration of elastase by comparison with an enzyme standard. Three tests were run together with a control in which incubation was undertaken without alginate being

present. All tests with alginate were carried out with the same incubation volume to alginate weight ratio.

Figure 2.1 shows the results in which the elastase solution was incubated with alginate for three hours. The control was incubated without alginate. All incubations with alginate were carried out with the same incubation volume to alginate weight ratio as described above. The data from three independent experiments are shown.

It will be seen that the enzyme activity remaining in solution was considerably reduced in comparison to the control in which the enzyme was incubated in identical conditions but without alginate.

Alginate fibrous material (Kaltostat®) was also found to have a better ability than gauzes to retain proteinases that were soaked into the dressing. To study this attribute, the procedure of Example 1 was followed but replacing the AQUACEL® with Kaltostat®. Figure 2.2 shows that the amount of elastase activity that was recovered in the washing supernatant was significantly lower in Kaltostat® (column D) than comparator dressing materials. These were a standard surgical gauze (column A), NA™ gauze (column B) and a highly absorbent commercially-available surgical dressing (Allevyn™) (column C).

KALTOSTAT® is a trade mark.

EXAMPLE 3

Alginate with a high mannuronic acid content (high-M alginate) has a different gelling characteristic from that of high guluronic content alginate (high-G content) (such as that used in Example 2) upon hydration.

The test materials were cut to provide a small amount of material (5 mg) which was then tested as in Example 2.

The results, shown in Figure 3, demonstrate that the enzyme activity remaining in solution was considerably reduced in comparison to the control in which the enzyme was incubated in identical conditions but without the high-M alginate. All incubations with high-M alginate were carried out with the same incubation volume to alginagte weight ratio as described in Example 2.

EXAMPLE 4

A composite fibrous material containing 45% alginate and 55% NaCMC was produced in accordance with Example 1 of International Patent Publication WO 97/39170.

This composite fibrous material was then tested as in Example 2 but for an incubation period of one hour only. Like tests were also made with AQUACEL® and with Kaltostat®. All tests with alginate were carried out with the same incubation volume to alginate weight ratio.

The results, shown in Figure 4.1, demonstrate that when this composite material is incubated with an elastase solution for one hour, the residual elastase activity in solution is considerably reduced (column C) beyond that achieved by incubation with the same weight of alginate alone (column B), or with the same weight of NaCMC alone (column D). The control (column A) was incubated without added material.

An additional mixed fibre composition containing alginate and sodium CMC in the ratios of 60%:40% (AC6040) was also produced in

accordance with Example 1 of International Patent Publication WO 97/39170. This composite fibrous material was tested as in Example 1. The comparator dressing materials were two gauze materials (standard surgical gauze and NA™ gauze); a highly absorbent commercially available surgical dressing (Allevyn™); pure alginate (A100) and; pure sodium CMC (C100).

The results, shown in Figure 4.2, demonstrate that the amount of elastase activity that was recovered in the washing supernatant in formulation AC6040 was negligible and significantly lower in comparison to pure preparations of alginate (A100) and pure sodium CMC (C100). This shows an improved ability to retain the elastase in the fibres. The ability of the pure preparations to retain elastase was, in turn, superior to that of the comparator gauze dressing materials and Allevyn™. The combined data shown in Figures 4.1 and 4.2 indicate that the composite materials consisting of alginate and sodium CMC, with alginate at or in excess of 40% of the total fibre content, had superior proteinase absorption and retention capability.

In pathological conditions where proteinases are known to be a cause of tissue damage, these alginate-sodium CMC compositions may contribute to reducing the concentration of free proteinase by effective sequestration of these enzymes, and thereby contribute to reducing tissue breakdown. This is likely to be particularly appropriate in chronic wound conditions.

EXAMPLE 5

Mixed fibre compositions containing alginate and sodium CMC in the ratios of 30%:70% (AC3070), 50%:50% (AC5050) and 60%:40% (AC6040) were produced in accordance with Example 1 of International Patent Publication WO 97/39170. These mixed fibre compositions were

additionally mixed with cellulosic fibres to form non-woven fabrics using a standard needled non-woven process with the following compositions:

Formulation	Alginate (A)/CMC(C) Fibre	Cellulosic (L) Fibres	Final Composition
ACL 061480	20% AC3070	80%	A(6%), C(14%), L(80%)
ACL 101080	20% AC5050	80%	A(10%), C(10%), L(80%)
ACL 245620	80% AC3070	20%	A(24%), C(56%), L(20%)
ACL 252550	50% AC5050	50%	A(25%), C(25%), L(50%)
ACL 302050	50% AC6040	50%	A(30%), C(20%), L(50%)
ACL 404020	80% AC5050	20%	A(40%), C(40%), L(20%)

The results, shown in Figure 5, demonstrate that the amount of elastase activity that is recovered in the washing supernatant in formulations ACL404020 and AC 6040 (Example 4) is negligible and significantly lower in comparison to pure preparations of alginate (A100) and pure sodium CMC (C100), showing improved ability to retain elastase in the fibres. The ability of the pure preparations to retain elastase was, in turn, superior to that of the comparator gauze dressing materials and Allevyn™. In both of these materials, the amount, by weight, of alginate is 40% or more.

In pathological conditions where proteinases are known to be a cause of tissue damage, these alginate-sodium CMC compositions with or without

added viscose (Lyocell™) may contribute to reducing the concentration of free proteinase by effective sequestration of these enzymes, and thereby contribute to reducing tissue breakdown. This is likely to be particularly appropriate in chronic wound conditions.

LYOCELL™ is a trade mark.

EXAMPLE 6

A composite fibrous material containing alginate and poly(N-vinylpyrrolidone) (PVP) in the ratio of 1:1 was produced as follows. Alginate/PVP fibre samples were spun from a dope solution containing 6% w/w of solids comprising a 50/50 mixture of sodium alginate and PVP in water. The dope solution was made by adding 120g of PVP (ex Aldrich, 10,000 Da MW) and 120g of sodium alginate (ex Kelco LF10 10/60D) to 3790g of deionised water. The mixture was stirred with a high-speed mixer until the ingredients had dissolved and the dope allowed to stand overnight to degas.

The degassed dope was then poured into a pressure vessel attached to a spinning rig. The dope was next pumped to the 400 jet spinneret of the spinning rig and the rig started. The spinneret was immersed in the spin bath of the rig, which contained a solution of 0.3 mol/dm^3 of calcium chloride. The fibres so produced were threaded over three rollers of the first godet and then over the rollers of a second godet. The resulting yarn was then passed through two baths of propan-2-ol, which were maintained at a concentration to dry the yarn. The yarn was then passed through a set of pinch rollers and wound onto cones.

Figure 6.1 shows that when this composite material is incubated with an elastase solution for one hour as in Example 4, the residual elastase

activity in solution is considerably reduced beyond that achieved by incubation with the same weight of alginate alone. As before, all incubations with alginate were carried out with the same incubation volume to material weight ratio. The alginate was Kaltostat® wound dressing ex ConvaTec.

The procedure of Example 1 was next repeated but replacing the AQUACEL® with the alginate: PVP mixture and with Kaltostat®. Figure 6.2 shows that the amount of elastase activity that was recovered in the washing supernatant was comparable to the comparator dressing materials, in this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially available surgical dressing (Allevyn™). When taking into account the proteinase absorptive capability as shown in Figure 6.1, this composition may also have a usefulness in modulating proteinase levels in the wound environment.

EXAMPLE 7

A composite fibrous material containing 42.5% alginate, 52.5% NaCMC and 5% HYAFF (a benzyl ester of hyaluronic acid) was spun from a dope solution containing 6% w/w of solids in water. The dope solution was made by adding 102g of sodium alginate (ex Kelco LF 10/60D), 126g of NaCMC (ex Hercules Blanose 12MSP) and 12g of HYAFF powder (ex Fidia Biopolymers) to 3760g of deionised water. The mixture was stirred with a high-speed mixer until the ingredients had dissolved and the dope allowed to stand overnight to degas. It was then spun as in Example 6. It was then tested in the same manner.

Figure 7.1 shows that the alginate/CMC/HYAFF composite material has the ability to absorb elastase substantially better than that of insoluble alginates (Kaltostat®) and carboxymethyl cellulose (AQUACEL®).

Figure 7.2 shows that the amount of elastase activity that was recovered in the washing supernatant was comparable to the comparator dressing materials, in this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially-available surgical dressing (Allevyn™). When taking into the account the proteinase absorptive capability as shown in Figure 7.1, the composition may also have a usefulness in modulating proteinase levels in the wound environment.

EXAMPLE 8

A composite fibrous material containing 30% alginate, 60%NaCMC and 10% Pectin was spun from a dope solution containing 6% w/w of solids in water. The dope solution was made by adding 72g of sodium alginate (ex Kelco LF 10/60D), 144g of NaCMC (ex Hercules Blanose 12 MSP) and 24g of citrus pectin (ex Hercules) to 3760g of deionised water. The mixture was stirred with a high-speed mixer until the ingredients had dissolved and the dope allowed to stand overnight to degas. It was then spun as in Example 6. It was then tested in the same manner.

Figure 8.1 shows that the alginate/CMC/citrus pectin composite material has the ability to absorb elastase significantly better than that of AQUACEL®, Kaltostat® and Kaltogel®.

Figure 8.2 shows that the amount of elastase activity that was recovered in the washing supernatant was comparable to the comparator dressing materials, in this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially available surgical dressing (Allevyn™). When taking into the account the proteinase absorptive capability as shown in Figure 8.1, this composition may also

have a usefulness in modulating proteinase levels in the wound environment.

EXAMPLE 9

A composite fibrous material containing 70% alginate and 30% polyethylene oxide (PEO) was spun from a dope solution containing 6% w/w of solids in water. The dope solution was made by adding 180g of sodium alginate (ex Kalco LF 10/60D) and 60g of PEO (ex Aldrich, 100,000 Dalton MW) to 3760g of deionised water. The mixture was stirred with a high-speed mixer until the ingredients had dissolved and the dope allowed to stand overnight to degas. It was then spun as in Example 6. It was then tested in the same manner.

Figure 9.1 shows that alginate/PEO composite material has the ability to absorb elastase significantly better than that of AQUACEL®, Kaltostat®, Kaltogel® and fibrous gelling pectin.

Figure 9.2 shows that the amount of elastase activity that was recovered in the washing supernatant was comparable to the comparator dressing materials, in this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially available surgical dressing (Allevyn™). When taking into the account the proteinase absorptive capability as shown in Figure 9.1, this composition may also have a usefulness in modulating proteinase levels in the wound environment.

EXAMPLE 10

A composite fibrous material containing 50% GENU pectin and 50% citrus pectin was spun from a dope solution containing 10% w/w of solids

in water. The dope solution was made by adding 200g of GENU pectin (ex Hercules) and 200g of citrus pectin (ex Hercules) to 3600g of deionised water. The mixture was stirred with a high-speed mixer until the ingredients had dissolved and the dope allowed to stand overnight to degas. It was then spun as in Example 6. It was then tested in the same manner.

Figure 10.1 shows that the gelling pectin/citrus pectin composite material has the ability to absorb elastase significantly better than that of AQUACEL®, Kaltostat® and Kaltogel®.

Figure 10.2 shows that the amount of elastase activity that was recovered in the washing supernatant was comparable to the comparator dressing material, in this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially available surgical dressing (Allevyn™). When taking into the account the proteinase absorptive capability as shown in Figure 10.1, this composition may also have a usefulness in modulating proteinase levels in the wound environment.

EXAMPLE 11

A composite fibrous material containing 50% GENU pectin and 50% NaCMC was spun from a dope solution containing 10% w/w of solids in water. The dope solution was made by adding 200g GENU pectin (ex Hercules) and 200g of NaCMC (ex Hercules Blanose 12MSP) to 3600g of deionised water. The mixture was stirred with a high-speed mixer until the ingredients had dissolved and the dope allowed to stand overnight to degas. It was then spun as in Example 6. It was then tested in the same manner.

Figure 11.1 shows that the pectin/CMC composite material has the ability to absorb elastase comparable to that of Kaltostat® and Kaltogel®.

Figure 11.2 shows that the amount of elastase activity that was recovered in the washing supernatant was less that that of the comparator dressing materials, it this case two gauze materials (standard surgical gauze and NA™ gauze) and a highly absorbent commercially available surgical dressing (Allevyn™), indicating better enzyme retention. When taking into the account the proteinase absorptive capability as shown in Figure 11.1, this composition may also have a usefulness in modulating proteinase levels in the wound environment.

CLAIMS

1. A water-absorbent, composite material which comprises:

i) at least 30%, by weight of the composite material, of an alginate in admixture with:

ii) a hydrogel-forming, synthetic, non-polysaccharide polymer; and/or

iii) a mixture of at least two hydrogel-forming polymers different from ii).

2. A material according to claim 1 wherein the alginate comprises at least 40%, preferably at least 50%, by weight of the composite material.

3. A material according to claim 1 or 2 wherein the alginate has been rendered insoluble.

4. A material according to any preceding claim wherein the alginate comprises a major amount of mannuronic (high-M) moieties.

5. A material according to any preceding claim wherein ii) comprises a homo- or co-polymer of N-vinyl pyrrolidone, acrylamide or ethylene oxide.

6. A material according to any preceding claim wherein one of the components iii) comprises a semi-synthetic derivative of cellulose.

7. A material according to any preceding claim wherein one of the components iii) comprises cellulose, hyaluronic acid or a pectin.

8. A material according to any preceding claim wherein at least one of the components of i), ii) and/or iii) is a fibrous form.

9. A material according to claim 8 wherein at least two of the components are preparable by co-spinning.

10. A material according to claim 8 or 9 which is felted.

11. A material according to claim 8 or 9 which is woven or knitted.

12. A wound dressing which comprises a material according to any of claims 1 to 11.

13. Use of a composite material or polymer which is swellable in aqueous media for the manufacture of a wound dressing comprising the composite material or polymer to reduce the concentration of proteolytic enzyme in a wound by application of the wound dressing externally thereto.

14. Use according to claim 13 wherein the composite material is defined in any one of claims 1 to 11.

15. Use according to claim 13 wherein the polymer is a substituted or unsubstituted, homo- or co-polysaccharide.

16. Use according to claim 13 or 15 wherein the polymer comprises uronic acid groups.

17. Use according to any preceding claim 13, 15 or 16 wherein the substituted polysaccharide comprises etherified or acylated hydroxyl groups.

18. Use according to any preceding claim 13, 15, 16 or 17 wherein the substituted polysaccharide comprises esterified uronic acid groups.

19. Use according to any preceding claim 13 or 15 to 18 wherein the substituted polysaccharide comprises at least some hydroxyl groups which have been replaced by amino or acylated amino groups.

20. Use according to any preceding claim 13 or 15 to 19 wherein the substituent comprises a saturated or unsaturated, carbocyclic or heterocyclic, mono or polycyclic group.

21. Use according to claim 20 wherein the unsaturated group includes an aromatic group.

22. Use according to claim 20 or 21 wherein the polycyclic group comprises a fused polycyclic structure.

23. Use according to any preceding claim 13 or 15 to 22 wherein the polymer comprises a substituted hyaluronan.

24. Use according to any preceding claim 13 or 15 to 23 wherein the polymer comprises a substituted cellulose.

25. Use according to any preceding claim 13 or 15 to 24 wherein the polymer is cross-linked.

26. Use according to any preceding claim 13 or 15 to 25 wherein the polymer is formed as a film.

27. Use according to any preceding claim 13 or 15 to 25 wherein the polymer is formed as a fibre.

28. Use according to any preceding claim 13 or 15 to 27 wherein a mixture of polymers as defined in any of claims 13 or 15 to 26 is used in the manufacture of the wound dressing.

29. Use according to claim 27 wherein the fibres are disposed in the wound dressing manufactured therefrom as a non-woven mat or as a woven fibre.

30. Use according to any preceding claim 13 to 29 wherein the materials in the wound dressing manufactured therefrom are associated with one or more non-water swellable materials.

31. Use of a polymer according to any of claims 13 and 15 to 28 as a wound dressing agent.

32. A method of treatment of the human body, which method comprises applying externally to a wound on the body a wound dressing which comprises a composite material or a polymer which is swellable in aqueous media, the application thereby reducing the concentration of protease enzymes in the wound.

33. A method according to claim 32 wherein the composite material or the polymer is defined in any one of claims 28 to 31.

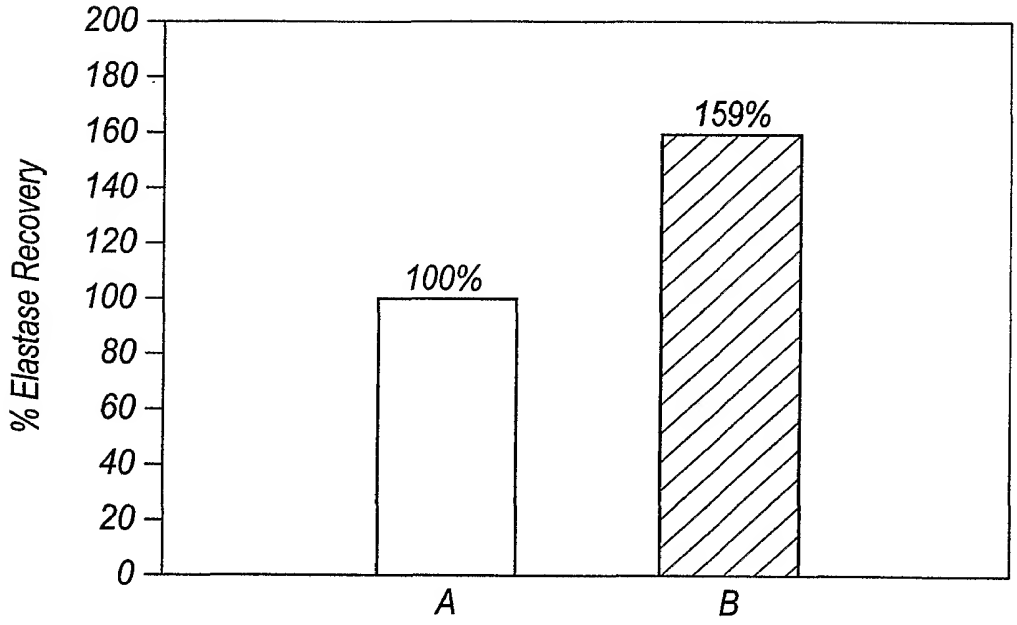
200
180
160
140
120
100
80
60
40
20
0
% Elastase Recovery
100%
159%
A
B

Fig.1

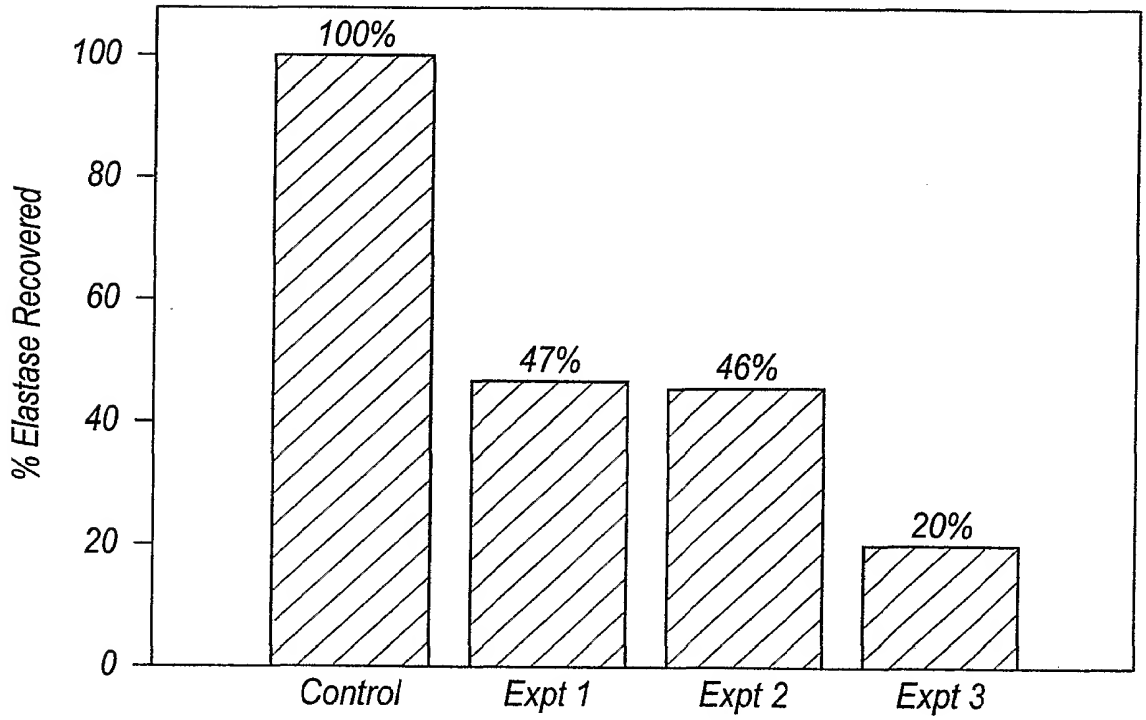
100
80
60
40
20
0
% Elastase Recovered
100%
47%
46%
20%
Control
Expt 1
Expt 2
Expt 3

Fig.2.1

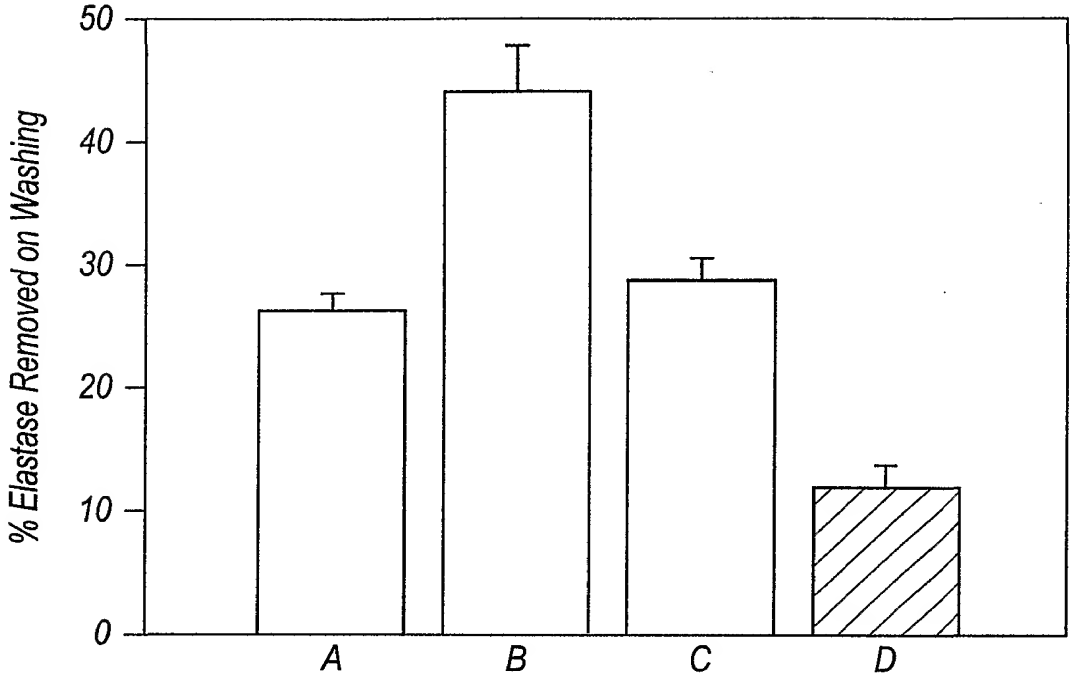
50
40
30
20
10
0
% Elastase Removed on Washing
A
B
C
D

Fig.2.2

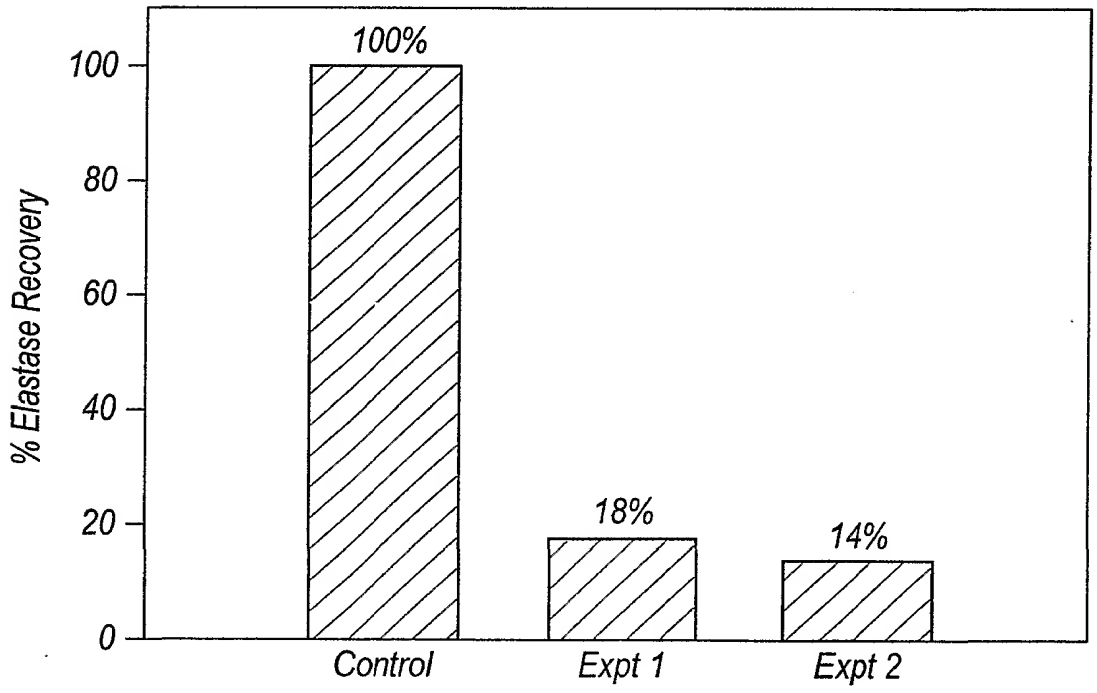
100
80
60
40
20
0
% Elastase Recovery
100%
18%
14%
Control
Expt 1
Expt 2

Fig.3

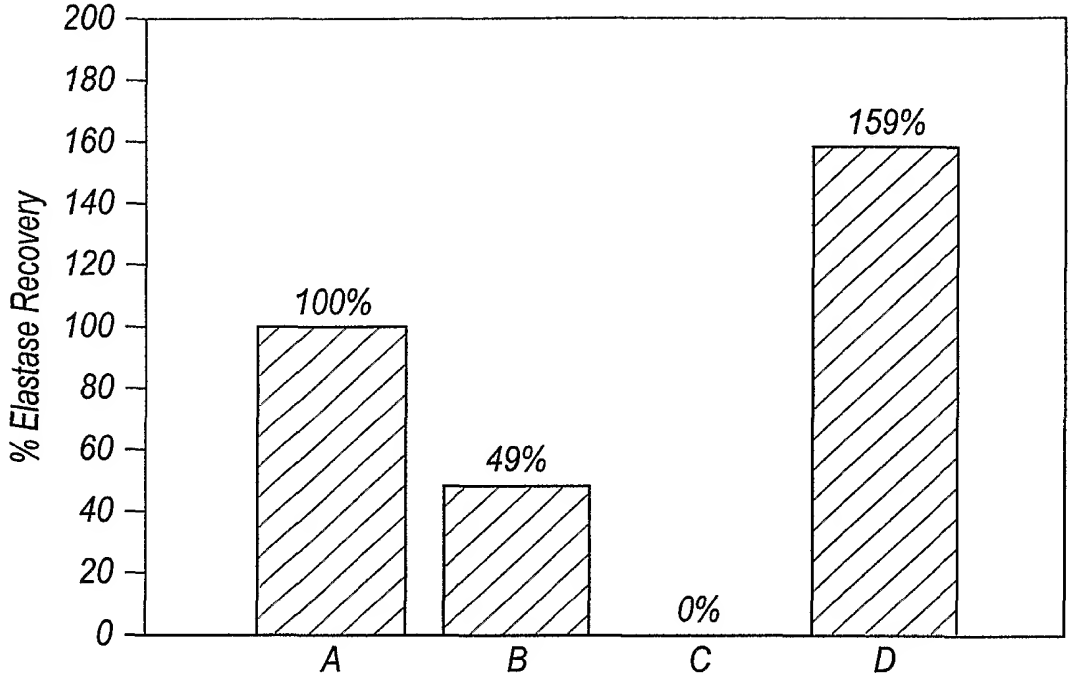
% Elastase Recovery
200
180
160
140
120
100
80
60
40
20
0
100%
49%
0%
159%
A
B
C
D

Fig.4.1

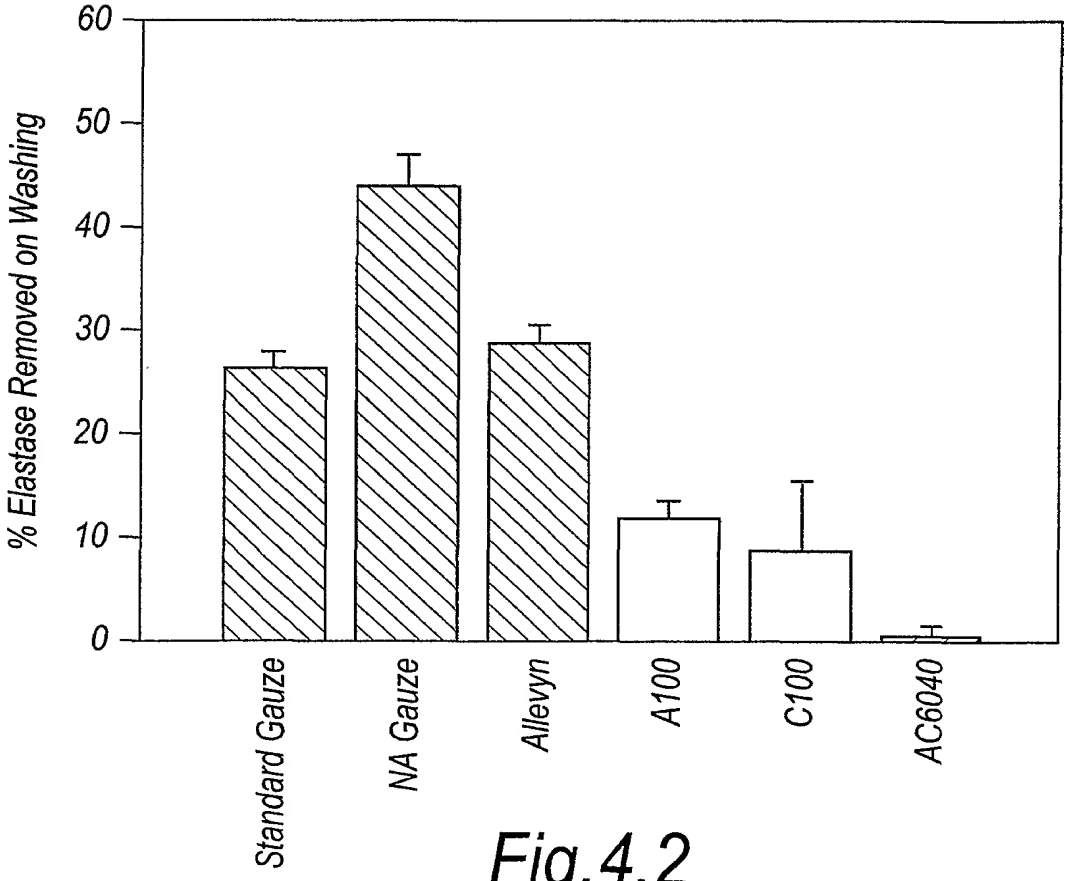
% Elastase Removed on Washing
60
50
40
30
20
10
0
Standard Gauze
NA Gauze
Allevyn
A100
C100
AC6040

Fig.4.2

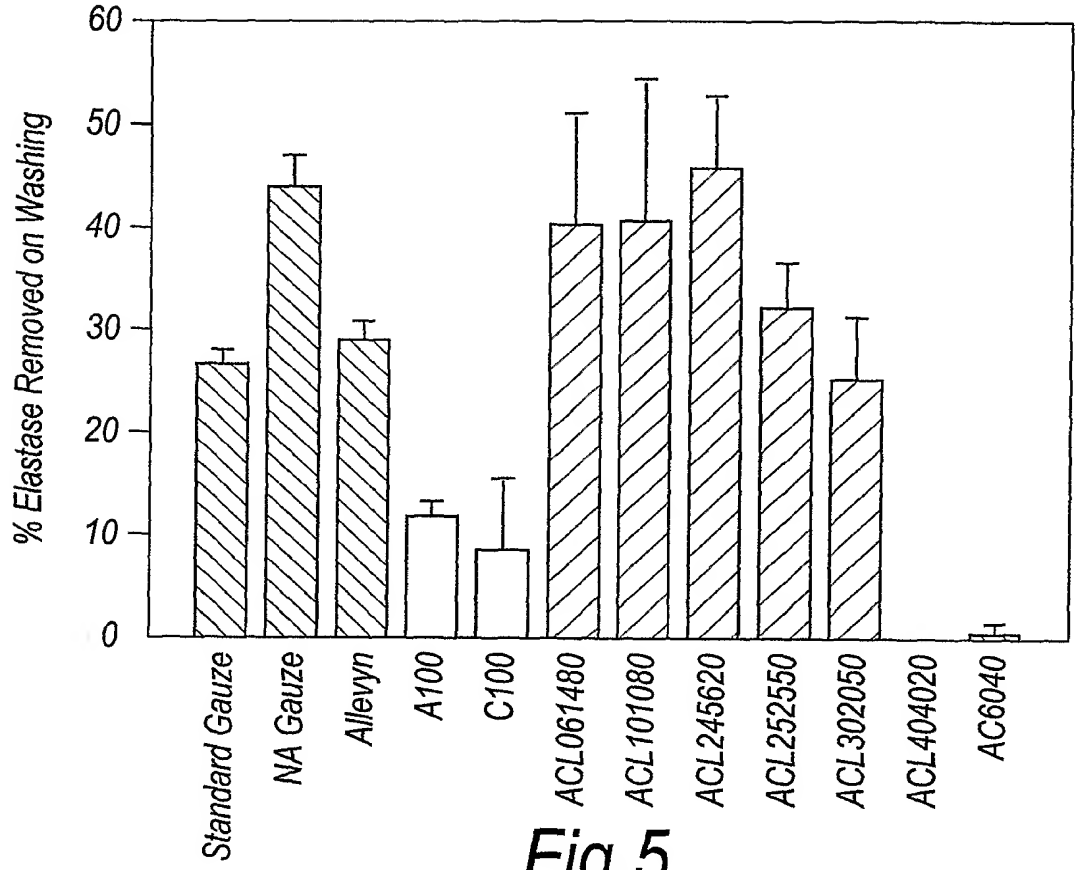
% Elastase Removed on Washing
60
50
40
30
20
10
0
Standard Gauze
NA Gauze
Allevyn
A100
C100
ACL061480
ACL101080
ACL245620
ACL252550
ACL302050
ACL404020
AC6040

Fig.5

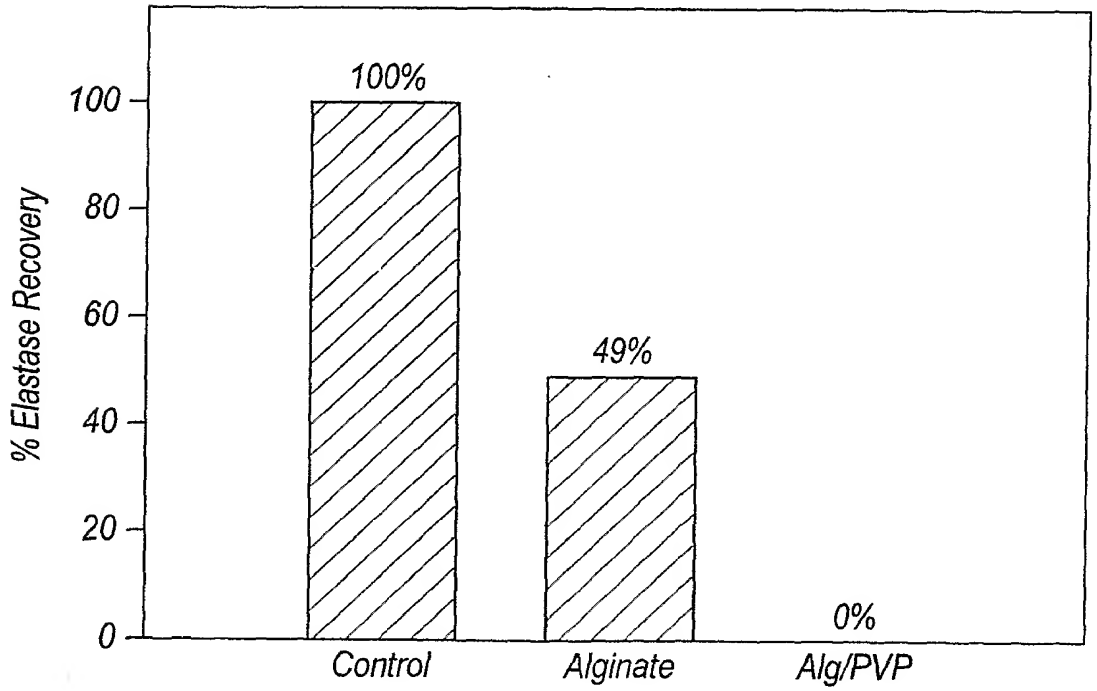
% Elastase Recovery
100
80
60
40
20
0
100%
49%
0%
Control
Alginate
Alg/PVP

Fig.6.1

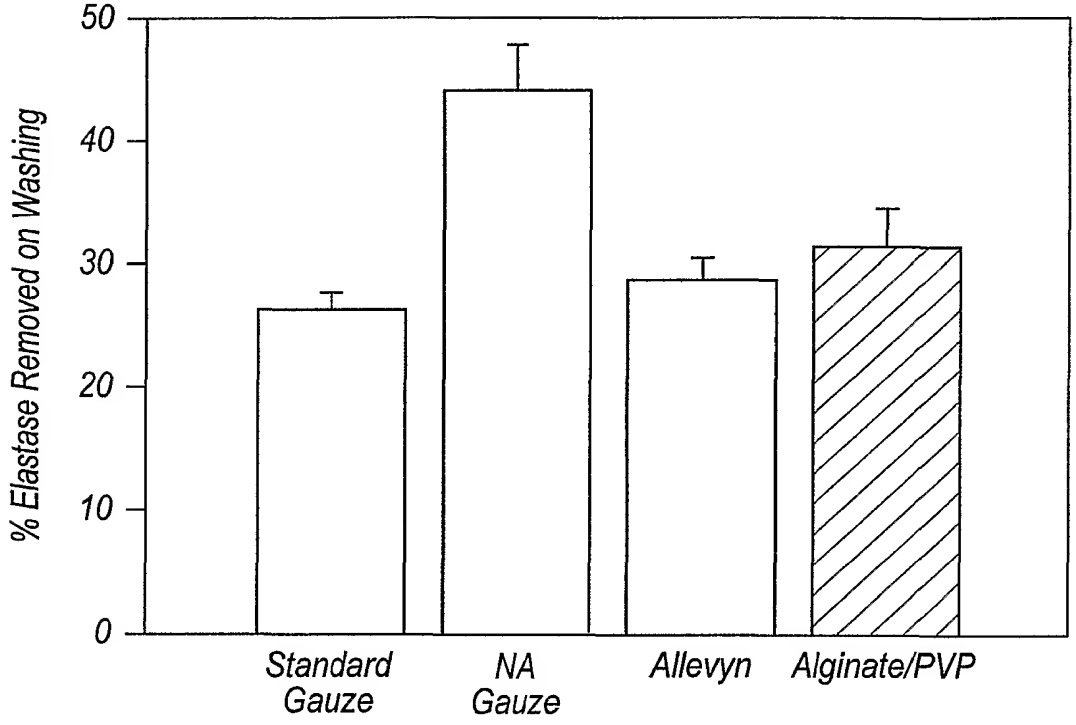
% Elastase Removed on Washing
50
40
30
20
10
0
Standard Gauze
NA Gauze
Allevyn
Alginate/PVP

Fig.6.2

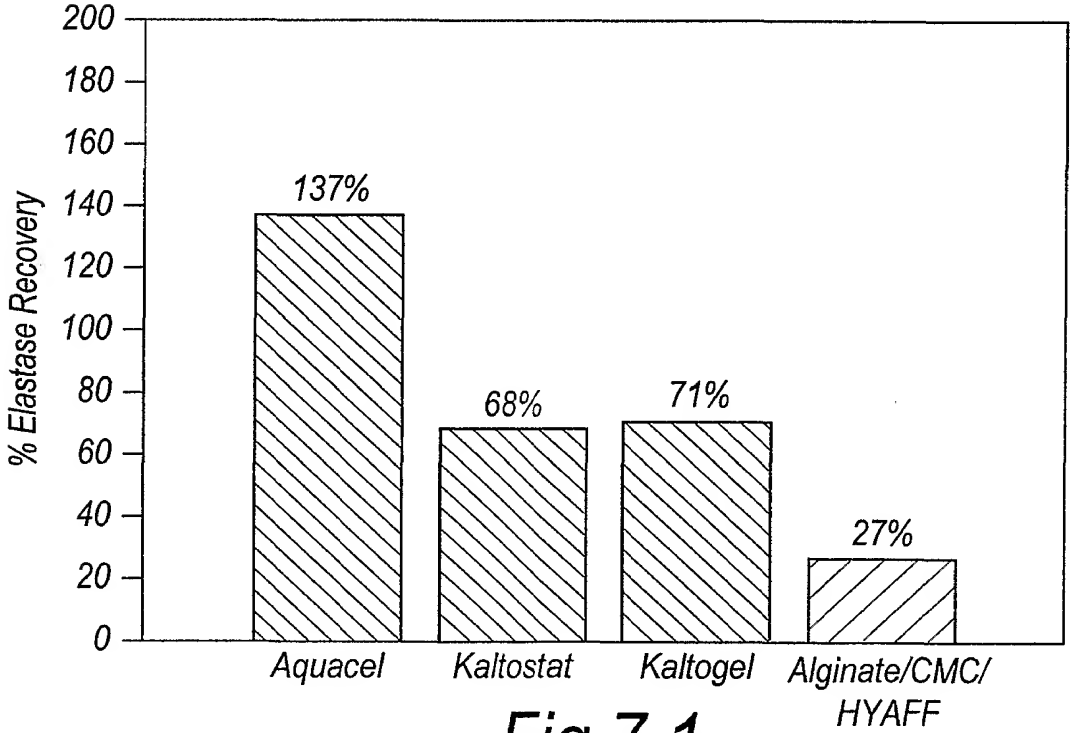
% Elastase Recovery
200
180
160
140
120
100
80
60
40
20
0
137%
68%
71%
27%
Aquacel
Kaltostat
Kaltogel
Alginate/CMC/ HYAFF

Fig.7.1

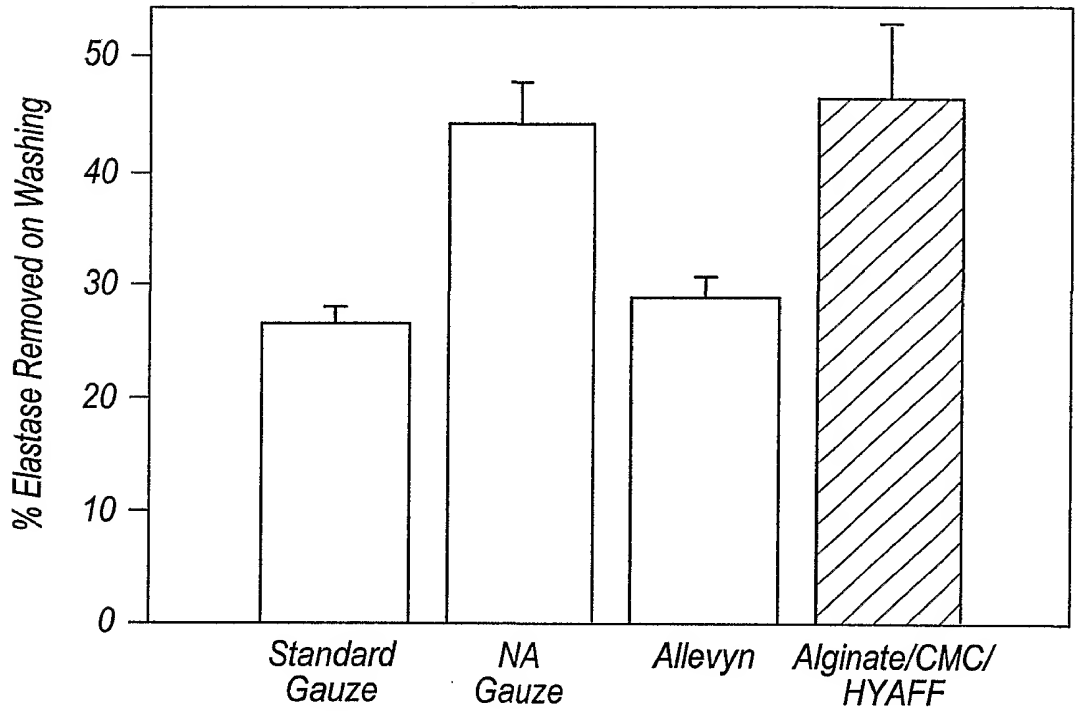
% Elastase Removed on Washing
50
40
30
20
10
0
Standard Gauze
NA Gauze
Allevyn
Alginate/CMC/ HYAFF

Fig.7.2

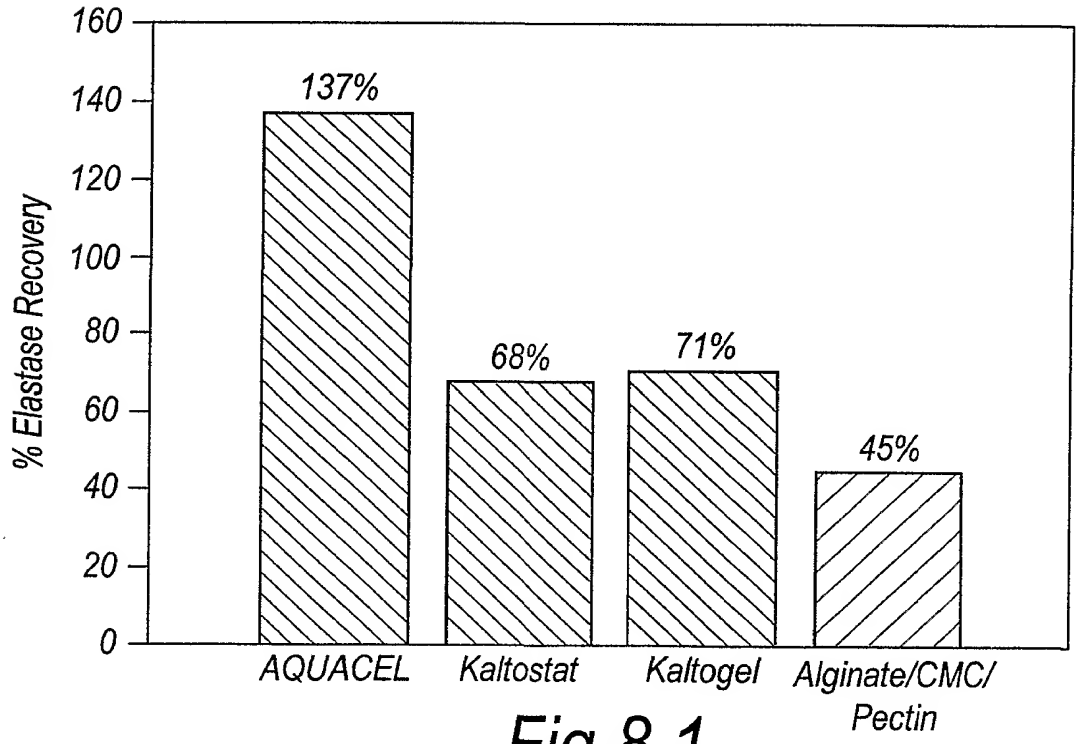
% Elastase Recovery
160
140
120
100
80
60
40
20
0
137%
68%
71%
45%
AQUACEL
Kaltostat
Kaltogel
Alginate/CMC/ Pectin

Fig.8.1

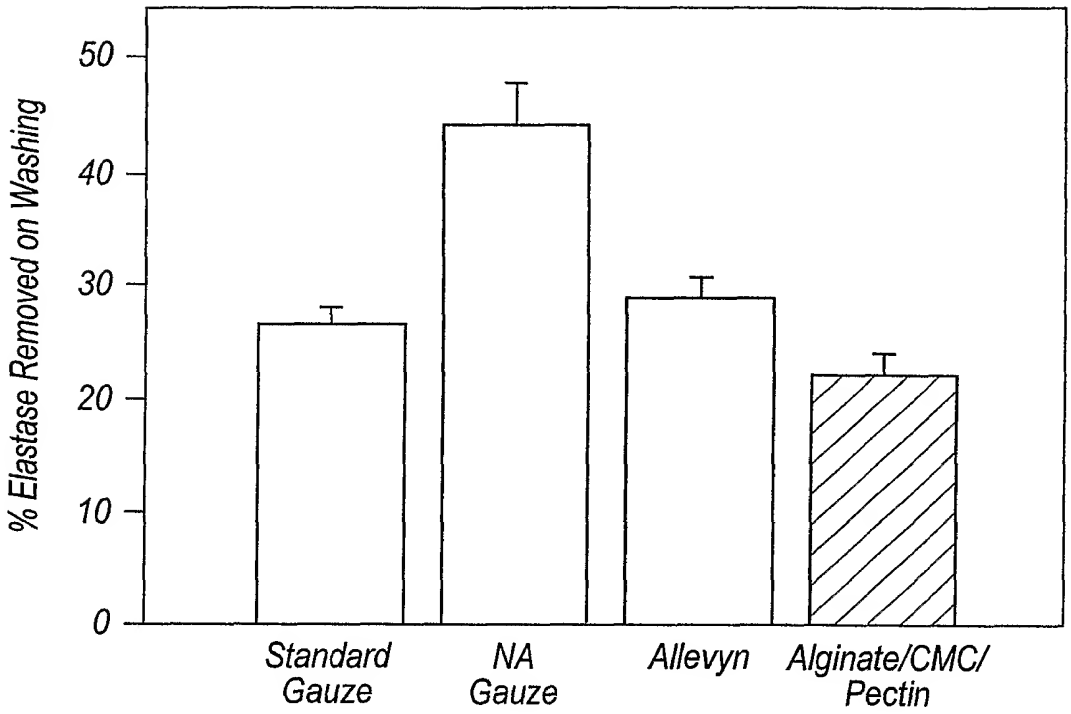
% Elastase Removed on Washing
50
40
30
20
10
0
Standard Gauze
NA Gauze
Allevyn
Alginate/CMC/ Pectin

Fig.8.2

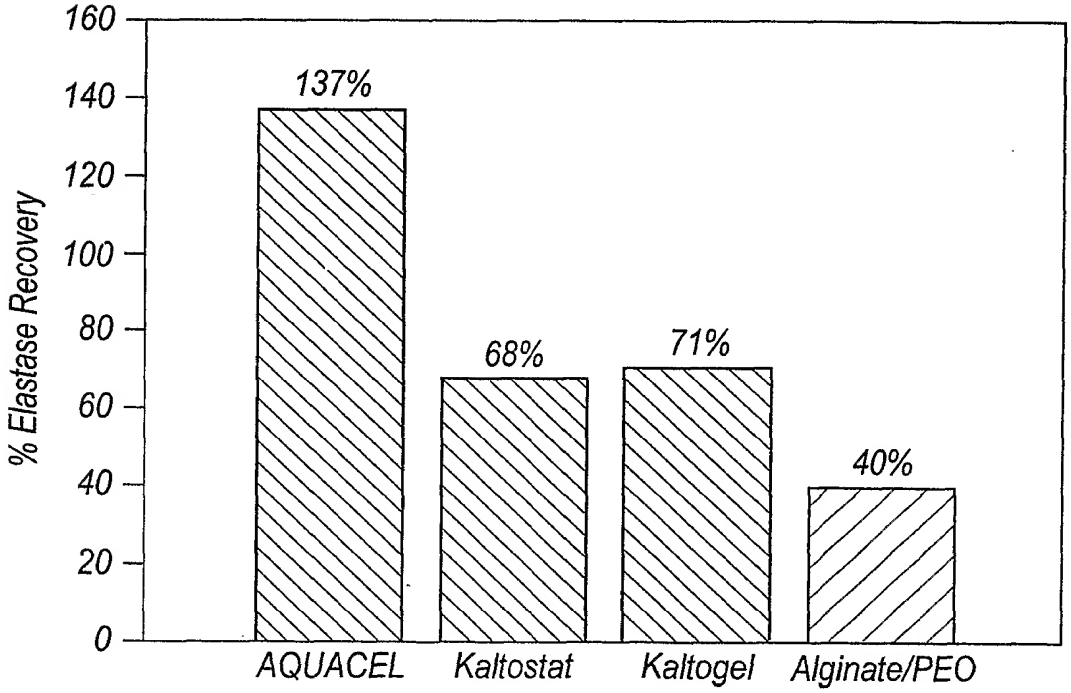
% Elastase Recovery
160
140
120
100
80
60
40
20
0
137%
68%
71%
40%
AQUACEL
Kaltostat
Kaltogel
Alginate/PEO

Fig.9.1

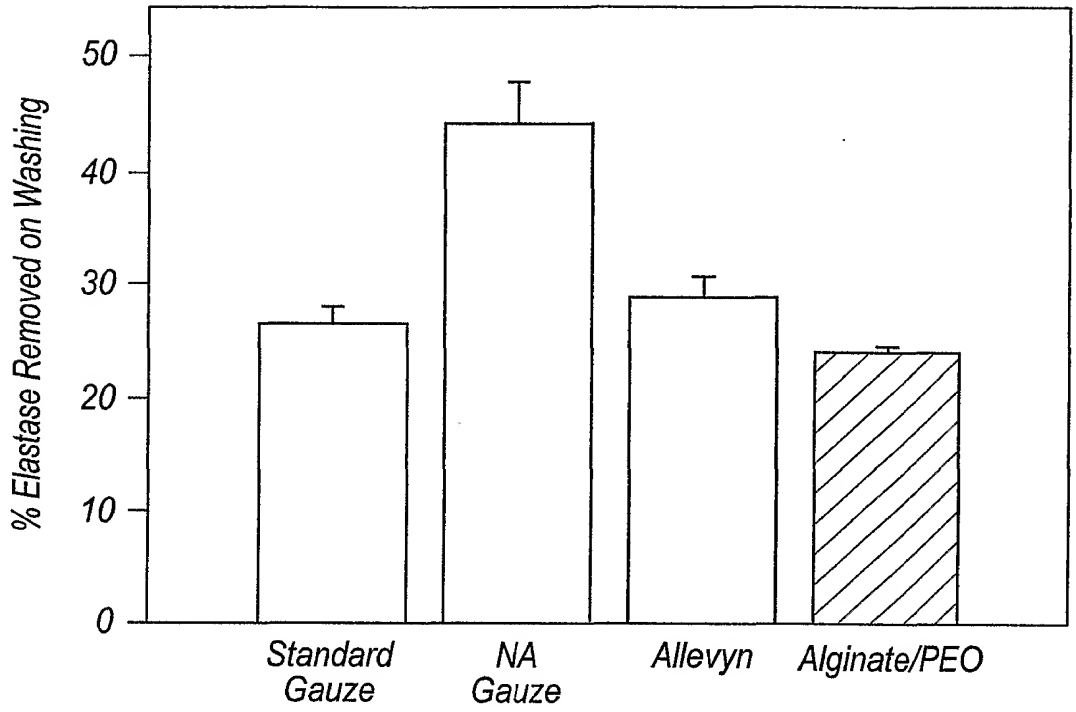

Fig.9.2

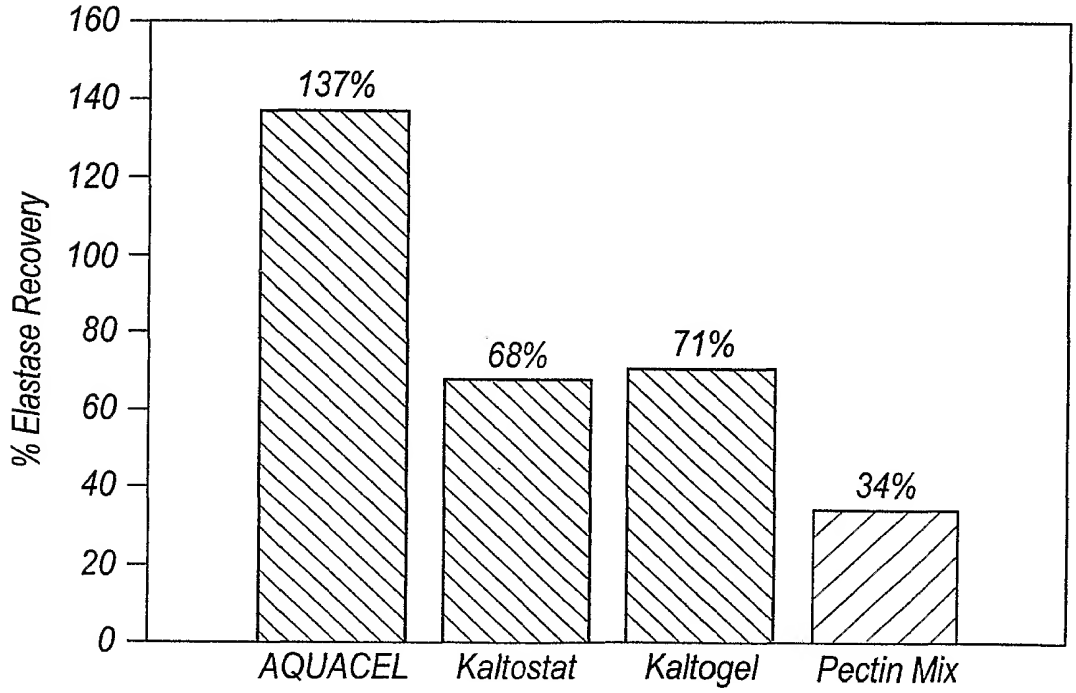

Fig.10.1

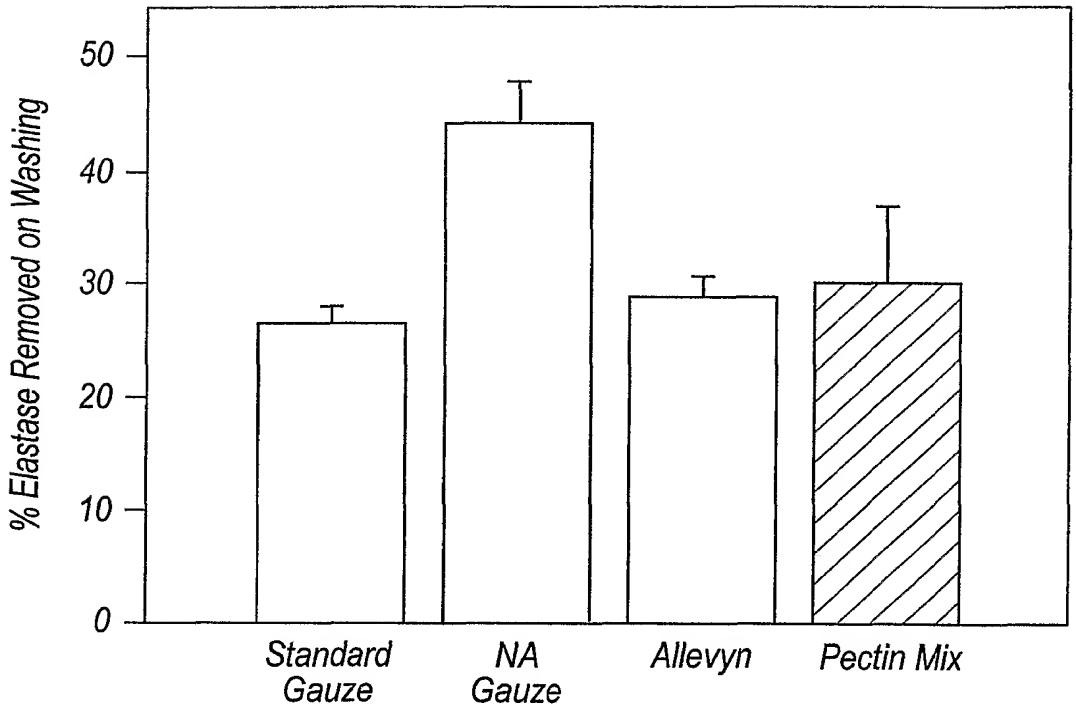

Fig.10.2

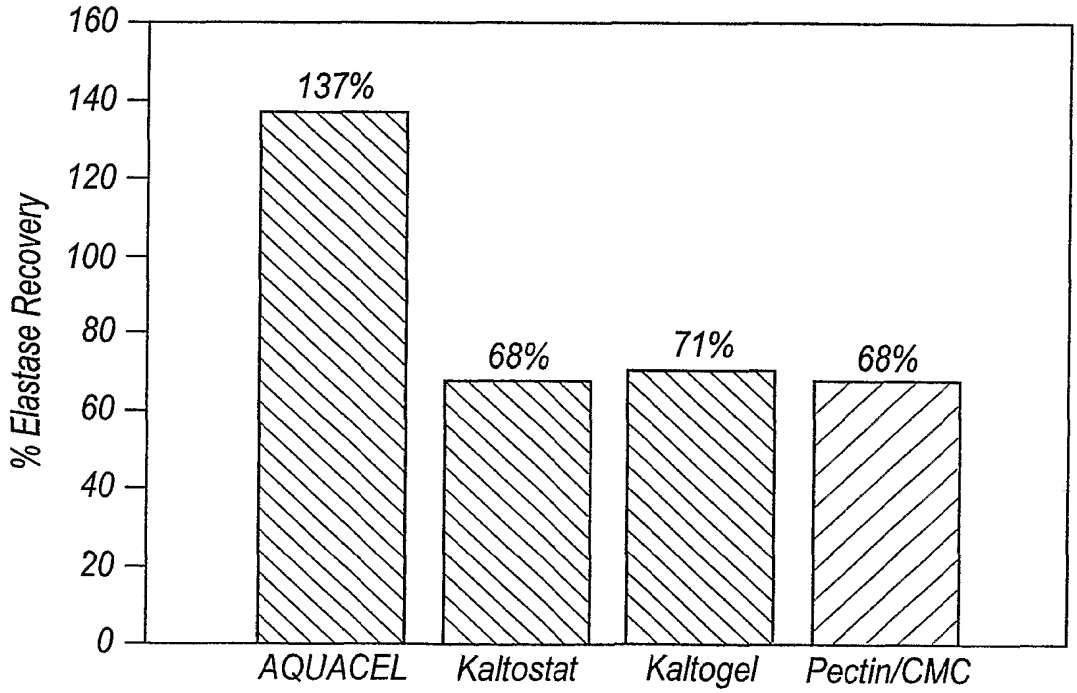

Fig.11.1

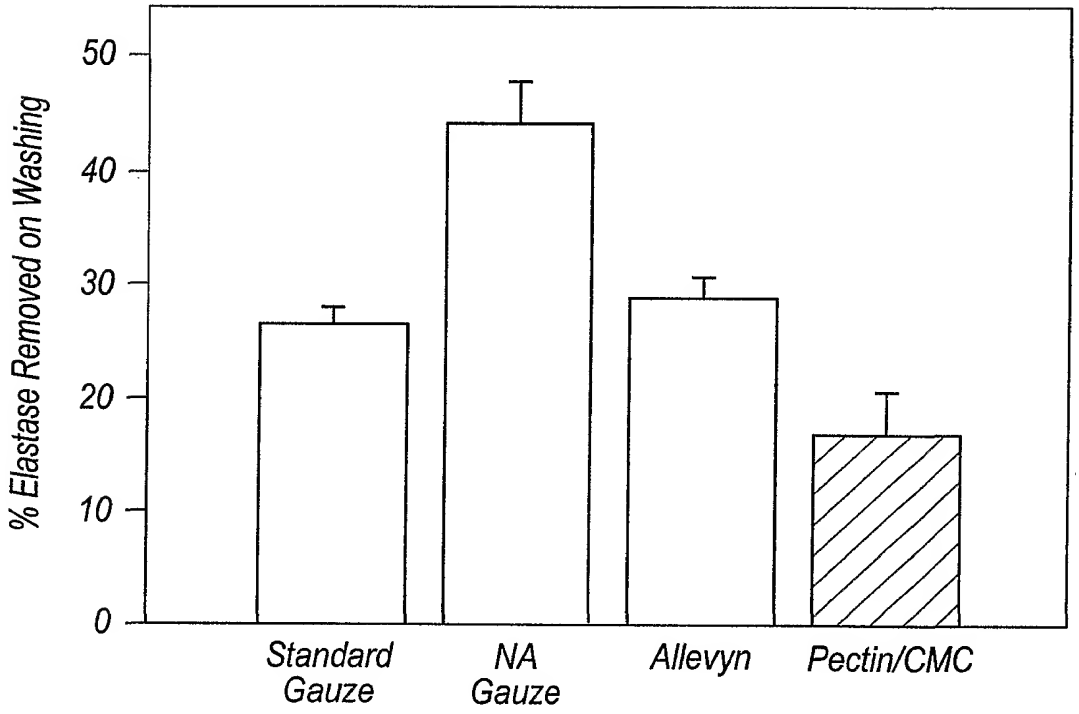
% Elastase Removed on Washing
50
40
30
20
10
0
Standard Gauze
NA Gauze
Allevyn
Pectin/CMC

Fig.11.2

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01573

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/00 A61L15/14 A61L15/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, COMPENDEX, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 329 693 A (WALLACE CAMERON CO LTD) 12 September 1973 (1973-09-12) example 6 claims	1-33
X	US 6 140 257 A (MAHONEY PETER M J ET AL) 31 October 2000 (2000-10-31) column 1, line 53 -column 3, line 5 examples 1-3 claims	1-33
X	WO 96 13282 A (INNOVATIVE TECH LTD ;QIN YIMIN (GB); GILDING KEITH DENNIS (GB)) 9 May 1996 (1996-05-09) page 2, line 6 -page 5, line 17 claims	1-33

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2002	14/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fey-Lamprecht, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 830 932 A (KAY DENNIS M) 3 November 1998 (1998-11-03) column 17, line 51 -column 18, line 16 claims	1-33
X	WO 99 01166 A (AYZMA JOSEF ;NIELSEN BRIAN (DK); COLOPLAST AS (DK); SCHOENFELDT LA) 14 January 1999 (1999-01-14) page 8, line 21 -page 10, line 22 claims	1-33
X	WO 98 09590 A (JACQUES ELIZABETH ;GRIFFITHS BRYAN (GB); BISHOP STEPHEN M (GB); SQ) 12 March 1998 (1998-03-12) page 1, line 32 -page 3, line 28 page 4, line 20 - line 32 example 1 claims	1-33
X	US 5 885 237 A (FRIGGLE HARRY B ET AL) 23 March 1999 (1999-03-23) column 3, line 41 -column 4, line 9 column 4, line 58 -column 5, line 12 claims	1-33
X	WO 98 46818 A (LYDON MICHAEL JAMES ;MAHONEY PETER M J (GB); COURT ANDREW D (GB);) 22 October 1998 (1998-10-22) page 4, line 10 -page 5, line 25 claims	1-33
P,X	WO 01 64132 A (US AGRICULTURE ;UNIV VIRGINIA COMMONWEALTH (US)) 7 September 2001 (2001-09-07) claims	1-33
X	US 5 688 923 A (GERRISH TIMOTHY C ET AL) 18 November 1997 (1997-11-18) claims	13-33
X	WO 91 11205 A (SKJAK BRAEK GUDMUND ;ESPEVIK TERJE (NO); SMIDSROD OLAV (NO); OTTER) 8 August 1991 (1991-08-08) claims	13-33

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/01573

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB 1329693	A	12-09-1973	NONE		
US 6140257	A	31-10-2000	AT	202388 T	15-07-2001
			AU	711723 B2	21-10-1999
			AU	2637897 A	07-11-1997
			DE	69705303 D1	26-07-2001
			DE	69705303 T2	25-04-2002
			DK	892863 T3	24-09-2001
			EP	0892863 A1	27-01-1999
			JP	2000508385 T	04-07-2000
			NZ	332112 A	23-06-2000
			CA	2250473 A1	23-10-1997
			WO	9739170 A1	23-10-1997
			ES	2157568 T3	16-08-2001
WO 9613282	A	09-05-1996	AU	3706695 A	23-05-1996
			EP	0788378 A1	13-08-1997
			WO	9613282 A1	09-05-1996
			GB	2309909 A ,B	13-08-1997
US 5830932	A	03-11-1998	US	5827247 A	27-10-1998
			US	5263947 A	23-11-1993
			AU	1290295 A	13-06-1995
			EP	0730437 A1	11-09-1996
			WO	9514448 A2	01-06-1995
			AT	160928 T	15-12-1997
			AU	2496092 A	16-03-1993
			CA	2115757 A1	04-03-1993
			DE	69223517 D1	22-01-1998
			DE	69223517 T2	16-07-1998
			DK	599995 T3	24-08-1998
			EP	0599995 A1	08-06-1994
			ES	2114567 T3	01-06-1998
			JP	6509956 T	10-11-1994
			WO	9303690 A1	04-03-1993
WO 9901166	A	14-01-1999	AU	7908798 A	25-01-1999
			WO	9901166 A1	14-01-1999
			EP	0994733 A1	26-04-2000
WO 9809590	A	12-03-1998	AU	716252 B2	24-02-2000
			AU	4622197 A	26-03-1998
			CN	1235533 A	17-11-1999
			WO	9809590 A1	12-03-1998
			EP	0927013 A1	07-07-1999
			JP	2000517226 T	26-12-2000
US 5885237	A	23-03-1999	AT	170396 T	15-09-1998
			AU	696877 B2	17-09-1998
			AU	7440994 A	27-04-1995
			CA	2132657 A1	06-04-1995
			DE	69412966 D1	08-10-1998
			DE	69412966 T2	14-01-1999
			DK	651983 T3	31-05-1999
			EP	0651983 A1	10-05-1995
			ES	2122150 T3	16-12-1998
			FI	944598 A	06-04-1995
			JP	7163615 A	27-06-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/01573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5885237 A		NO 943709 A	06-04-1995
		NZ 264583 A	26-03-1996
		ZA 9407574 A	28-03-1995
WO 9846818 A	22-10-1998	WO 9846818 A1	22-10-1998
		AU 719928 B2	18-05-2000
		AU 2386297 A	11-11-1998
		EP 0925396 A1	30-06-1999
		JP 2000510539 T	15-08-2000
		US 6268544 B1	31-07-2001
WO 0164132 A	07-09-2001	AU 4330901 A	12-09-2001
		WO 0164132 A2	07-09-2001
		US 2002064551 A1	30-05-2002
		US 2002012693 A1	31-01-2002
US 5688923 A	18-11-1997	AU 1976297 A	02-09-1997
		CA 2246703 A1	21-08-1997
		EP 0880547 A1	02-12-1998
		JP 2000504772 T	18-04-2000
		WO 9730093 A1	21-08-1997
WO 9111205 A	08-08-1991	AU 7221691 A	21-08-1991
		WO 9111205 A1	08-08-1991